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REGENERATIVE MEDICINE REGULATION: GLOBAL ISSUES AND ARGENTINE OPPORTUNITIES

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Policy Brief 1:2011

Drawing on a 2-day interactive expert workshop held on 7-8 November 2011 at the ESRC Genomics Forum in Edinburgh under the Forum's Bright Ideas Programme, and also drawing on interdisciplinary engagements between interested stakeholders in the Argentine and UK regenerative medicine field that have been ongoing for some four years, this Policy Brief explores key issues in the regulation of cellular products, and, drawing on the EU and UK experience, makes a number of recommendations for regulation in Argentina.

THE POLICY WORKSHOP & WORKING GROUP

Scholars, regulators and other key actors in the Argentine and UK regenerative medicine field have been mutually engaged for some four years now. Most recently, Fabiana Arzuaga (Arzuaga) was hosted by the ESRC Genomics Forum under its Bright Ideas Programme.¹ On 7-8 November 2011, Arzuaga and Shawn Harmon (Harmon), with support from the Genomics Forum, organised a 2-day interactive workshop with experts and scholars interested in the field (Working Group).² The aims of the workshop were to:

- explore the evolving regulatory state of affairs for regenerative medicine and cellular therapies in Argentina;
- report on the findings of the Governing Emerging Technologies: Social Values and Stem Cell Regulation in Argentina project;³

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¹ See <http://www.genomicsnetwork.ac.uk/forum/>.

² In addition to Arzuaga and Harmon, the Working Group consisted of Prof. Graeme Laurie, Prof. Joyce Tait (Innogen), Iain Gillespie (former OECD), John Purves (former EMA), Dr. Steve Sturdy (Genomics Forum), Dr. James Mittra (Innogen), and Ms. Carol George (SCRIPT).

³ See <http://www.law.ed.ac.uk/ahrc/esrcvaluesproject/>.

- draw on the experience of the UK and Europe with a view to formulating recommendations for proceeding in Argentina; and
- offer participants an opportunity to reflect on the robustness of UK and EU regulatory mechanisms.

After presentations from Arzuaga (on the Argentine social and regulatory context), Harmon (on the Argentine empirical data concerning values and regulatory ambitions), and John Purves (Purves)(on the EU medicinal products framework), the Working Group structured an open discussion around three live questions:

1. What is the impact of law on innovation, and how might law be fashioned so it avoids inhibiting innovation?
2. Is the UK/EU model for dealing with Advanced Therapy Medical Products (ATMPs) for hospital exemptions, whereby stem cell therapies can be administered to individual patients within a hospital using GMP practices, suitable for Argentina?
3. Are cellular based materials best characterised as drugs, devices, transplant tissue, or a *sui generis* substance?

After some wide-ranging discussions which took into consideration the international nature of science, the empirical evidence generated by the GET: Social Values Project (undertaken by Harmon and Arzuaga), and the specific experience of the participants, the following findings were reached generally agreed.

DISCUSSION & FINDINGS

Definitions & Boundaries

Cellular products will (eventually), if the science progresses as desired, fall under different regulatory categories: they may be tissue that is transplanted, they may be medicinal products subjected to an manufacturing procedure, and they may also be combined with mechanical devices that are operated within and outwith the body. They have (and will have) a unique nature.⁴ Thus, one issue in cellular products that requires careful consideration is definitions and product classifications and the boundaries between transplants and medicinal products. The matter of classification is not yet settled.

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⁴ We are probably 15+ years away from cellular therapies that are anything more than patient-specific treatments, and we are farther off from therapies that are suitable for pharmacy-type trials and distribution.

The EU, through the European Medicines Agency (EMA), has classified cellular products as Advanced Therapy Medicinal Products (ATMPs). Its approach, which draws on an array of Regulations, Technical Directives, and Guidelines, relies on early contact between regulators and industry to address matters of product classification, scientific uncertainty, and product certification for quality and non-clinical aspects. Unfortunately, the European approach is rather fragmented (as evidenced by difficulties associated with clinical trials of cellular products).

With respect to classifying some cellular products as ATMPs and thereby giving them operative space under the 'hospital exemption', Europe has experienced significant individual- or practitioner-based innovation in the devices field, which the hospital exemption was intended to permit, but there is no evidence of these innovations leading to practices that have been more broadly taken up, a fact which may not be surprising given the stage of scientific understanding, the availability of resources for product development, and the difficulty of transitioning to clinical trials.

Discourse & Engagement

There is a tension between the desire for regulatory certainty and the need for regulatory flexibility. In the cellular therapies setting, there is significant scientific/technical uncertainty, and so there will inevitably be regulatory uncertainty. This makes communication between and amongst stakeholders essential. The idea of open communications and debate is essential. Transparency is important for all stakeholders, to know who the other the stakeholders are and to consistently engage with them.

The EU strength has been its recognition that the field will benefit from detailed consultation with ALL interested parties and that the evolution of scientific understanding will rely in no small part on the market (ie: the regulatory framework must not only address supply issues, but also demand issues and pressures as well). The EU orphan drug regime is a good example of collectively tackling a problem rather than developing labyrinthine structures, and it is an approach that has been adopted for ATMPs. The EU medicinal products regulatory system has evolved and a key to that evolution has been the involvement of patient/interest groups (ie: non-industry actors), who remain important 'thinkers' (although leadership must come from the Ministers of Health and/or Science).

There are many barriers to bringing a product to market; in addition to scientific uncertainty, there are financial pressures, questions about how cellular products might be tested (deployed in clinical trials and under clinical trial regulation), and so on. Policymakers must be aware of how different considerations and regimes affect basic science and its transition to applied science (eg: marketing or market access regulation and commercialisation

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regulation are all relevant). Thus, it is useful for policymakers to consider how innovators are looking forward to markets, and to map routes into that market; again, this reflects the need to have open lines of communication between regulators and stakeholders (understood in the widest sense). Open communication (including scientific exchange) needs to be encouraged around issues of quality, safety, and efficacy, as well as values and social objectives.

Argentina might avoid the sense that the landscape is always shifting by encouraging communication and measuring stakeholder experiences, all of which will be helpful in terms of risk identification and management, including risks associated with investment. Communication serves as a shaping tool; even if some instruments within the regulatory framework are sub-optimal (because they articulate expectations at a point in time), communication permits scientifically-grounded changes to be negotiated.

Goal-Oriented Regulation

Regulatory frameworks must be alive to new scientific innovations, but their responses to these innovations must be conservative, taking account of their primary duty to public health and the control of quality, safety, and efficacy of medicinal products. Technocratic reactions to new scientific insights tend to be cumulative; they lead to new levels of oversight and therefore to increased regulatory load. The Working Group was unable to identify an example where regulatory load was *reduced* as a result of technical developments or reflexively examining the field and saying ‘this isn’t working any more’.⁵ Importantly, increased regulatory demands (including increased data submitted by industry and increased data demands to satisfy regulatory hurdles) have not, on the whole, resulted in better decisions or more innovation, when regulators made decisions on much smaller dossiers, medicines were approved and no great catastrophes were suffered.⁶

While fragmentation of decision-making, accumulation of regulatory load, and inflexibility of frameworks hampered the EU in the early days (1975-1985), and to some extent remain ongoing challenges, the value of harmonisation amongst the member states is demonstrated by the development of common legislation and useful cross-jurisdictional debates which have led to harmonised approaches. This can only be achieved if there are clear social/regulatory objectives and a framework that transparently operates

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⁵ The idea behind GMO regulation in the EU was to start strict and at the lower level (ie: put regulatory criteria in annexes and through them require industry/scientific applicants to provide technical detail because regulators were unclear what they should be asking). The idea was that the specifics could be changed easily and this stringency could be reduced, but the reality is that the guidelines have been strengthened/toughened rather than clarified and streamlined.

⁶ Thus, it is difficult to see how an increased corpus of information has helped the regulatory processes (or helped science achieve its ends).

toward those objectives. One stated objective has been the EU's emphasis on strengthening the single market, which has meant that the system shepherds innovations toward the market. Here political leadership is important; 'checking in with the polity' lends it greater legitimacy when setting up evaluation procedures and making decisions about the sharing of risk burdens (both of which are part of an integrated quality management system).

Potential system designers like Argentina might take notice of the requirements of the International Conference on Harmonisation (ICH – started in 1990), which will be important with respect to getting into the international scene; Argentina will need the provinces to come on board and join a uniform system. Additionally, Argentina may wish to acknowledge the importance and value of a uniform clinical trials framework. However, it should also recognise that novel materials (like cellular products) might need a different and more streamlined approach to clinical trials; the EU has been hampered in its clinical trials of novel materials because of the complexity of the responsibility of such trials being left to each member state, which adds to the development costs of clinical trials.

RECOMMENDATIONS

Argentina is in a unique and enviable position in that it has the opportunity to design a rational and streamlined cellular products system from the bottom up. Based on the discussions, the authors would recommend the following policy actions for Argentina:

- **Recommendation 1: A *Sui Generis* Framework:** Cellular products will begin as one thing (eg: something specialised for individual patients), and, as they are better understood, will become something else (eg: something mass produced for the public health setting), so regulation governing them might best be approached on a *sui generis* basis which does not mimic the terms and complexity of more *ad hoc* systems. The Working Group does not endorse the unaltered adoption of the EU approach, but there is value in being aware of the EU system so that a fit-for-purpose and internationally reliable Argentine system can be designed. A *sui generis* framework might adopt an holistic approach that provides guidance from basic research, through product development to product market and beyond, the broad view of which can allow Argentina to continue to improve the system and encourage innovation as science and understanding progress.
- **Recommendation 2: Regulatory Goals/Objectives:** Argentina should dwell less on the definitional aspect of regulation and more on the objective of regulation broadly based so as not to inhibit progress (ie:

"Political leadership will be important in designing a fit-for-purpose regulatory regime, and that regime must acknowledge core values and address primary responsibilities toward public health; this means controlling the quality, safety, and efficacy of medicinal products."

the regulatory goals). The objective must be to generate new knowledge and to develop new responses to disease and illness within a value environment that suits the polity (ie: it must be to encourage the ethical development of products that can efficiently be distributed throughout Argentina and international markets). In order to do so, key regulatory aims must be to: (1) articulate a broad value base (supported by the civil law); (2) explicitly promote innovation;⁷ (3) embed and specify quality standards for both research and products; (4) ensure safety of products for human application; (5) maximise (and test) the efficacy of products; and (6) identify and manage risk (which involves negotiated risk sharing).

- **Recommendation 3: Single Regulatory Entity:** A single entity tasked with regulating all aspects of regenerative medicine (from research to marketing of cellular products) may be optimal,⁸ but that entity would have to have value guidance, clear authority, and, supremely important, open lines of communication with ‘stakeholders’⁹ so that the framework can be co-produced. Open and ongoing communication between the stakeholders is vitally important so that parties can jointly work toward regulatory/social goals. This single entity should have a clear mission statement, a good management structure, and an integrated quality management system.
- **Recommendation 4: Harmonising Clinical Trials Law:** In addition to a regenerative medicine regime, Argentina needs a federal clinical trials law which is applicable to the provinces and serves to harmonise instruments and practices within the provinces, assuring protection of fundamental rights of the subjects of research.

The Working Group concluded that the problem isn’t knowing what the problem is but marshalling the political will to move, and knowing in what direction to move – Argentina is well placed because of its current political actors and growing technical/regulatory understanding.

"The Working Group does not endorse the unaltered adoption of the EU approach, but there is value in being aware of the EU system."

⁷ It was agreed that identifying innovation promotion, knowledge generation, innovation promotion, and treatment/therapy development as national goals in the preamble or recitals of a law is important because this signals core objectives, and creates expectations around the regulation. The philosophy of the framework should also be apparent (eg: will it be a light-touch system that can be modified through experience). This corresponds with our data from Argentina that stakeholders think the law should enumerate values and objectives.

⁸ A single entity with multiple roles will often be more efficient and effective than multiple entities with narrower roles which then have to coordinate.

⁹ Those who are being regulated, including industry, scientists/researchers, patient groups.